ABSTRACT OF THE DISCLOSURE

Therapeutic methods for inhibiting the growth of preneoplastic/ neoplastic vertebrate cells that abnormally express MN protein are disclosed. Screening assays are provided for identifying compounds, preferably membrane-impermeant compounds, which inhibit the enzymatic activity of MN protein/ polypeptides and that are useful for treating patients with preneoplastic/neoplastic disease. Further methods are disclosed for the preparation of positively-charged, membrane-impermeant heterocyclic sulfonamide CA inhibitors with high affinity for the membrane-bound carbonic anhydrase CA IX. Preferred CA IX-specific inhibitors are aromatic and heterocylic sulfonamides, preferably that are membrane-impermeant. Particularly preferred CA IX-specific inhibitors are pyridinium derivatives of such aromatic and heterocyclic sulfonamides. The CA IX-specific inhibitors of the invention can also be used diagnostically/prognostically for preneoplastic/neoplastic disease, and for imaging use, for example, to detect precancerous cells, tumors and/or metastases. The CA IX-specific inhibitors can be labelled or conjugated to radioisotopes for radiotherapy. The CA IX-specific inhibitors may be combined with conventional therapeutic anti-cancer drugs, with other different inhibitors of cancer-related pathways, with bioreductive drugs, or with radiotherapy to enhance the efficiency of each treatment. The CA IX-specific inhibitors may also be combined with CA IX-specific antibodies, preferably monoclonal antibodies or biologically active antibody fragments, more preferably humanized or fully human CA IX monoclonal antibodies or biologically active fragments or such monoclonal antibodies. Still further, the CA IX-specific inhibitors can be used for gene therapy coupled to vectors for targeted delivery to preneoplastic/neoplastic cells expressing CA IX on their surfaces.